December 16, 1962

Dear Alex:

I've just finished reading your review on somatic phases in plants, enjoyed it very much, and want to thank you for sending me the reprint. I had browsed into some of that literature when I was thinking about phase variation in Salmonella, and it is welcome to have it tied together as you have.

There is one point about the problem that still eldes me. Like yourself, I incline strongly to a paramutational (or epinucleic) interpretation of development, and would like to focus on the aptest experimental material. (Frustration about not reacting the chemistry of genetic transfer in Salmonella is what pushed us into Bacillus subtilis work-- where, so far, we have seen no phenomena of phase differentiation). Is there any particular evidence that the somatic phase in plants is even a cellular specificity (apart from its intracellular seat)? I could, for example, readily imagine that the inter-cellular pattern of the meristem could be self-propagating, and determine the phase. To answer this, one would have to show that an isolated cell has a definite phase, and I could find no indication about this in your review. Is there experimental material, showing phase variation, where one can propagate from an isolated cell of a meristem of either phase? (Transplant will do as well as explant propagation). I do believe that a definite answer to this issue is an essential next step. If it is not experimentally feasible, then I would have to question whether we are ready to penetrate much further into the problem with plant material.

Bruce

On the chemical side, we have to be thinking of more definite, especially testable models of what is happening to, or near, the DNA. Since the organization of chromosomes parallels the phylogenetic elaboration of somatic differentiation, we clearly do not have to rely entirely on changes in the polynucleotide itself, and I think one of the most attractive hypotheses is the simplest -- that some genes are broken, by nuclease action, at exposed nodes, and thus prevented from working in the further history of the clone. The breaks are not necessarily completely irreversible-- a repair enzyme might later reform the diester bridges. The weakness of this idea is its suppositions about chromosome structure -- visible, effective chromosome breaks must then be a special category of polynucleotide scissions. In plant material it is particularly provocative that the DNA cytosine is partly methylated, probably variably among different tissues. It would be very entertaining to see whether the distribution of methylcytosine was the same in DNA from alternative phases. The methylation almost certainly occurs after the synthesis of the polynucleotide; however, the control of formation of the methylating enzyme, among others, might depend on the methylation of the cytosine of the DNA of the corresponding gene. Again, the success of such an experiment depends on access to a good experimental system, not too much confounded with the metabolic consequences of the phase difference.

With best wishes,

As ever,

Joshua Lederberg

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